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## Improvement in Cranioplasty: Advanced Prosthesis Biomanufacturing

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## Abstract

Additive manufacturing (AM) is a technology that enables the production of models and prosthesis directly from the 3D CAD model facilitating surgical procedures, implant quality and reducing risks. Furthermore, the additive manufacturing has been used to produce implants especially designed for a particular patient, with sizes, shapes and mechanical properties optimized, in many areas of medicine such as cranioplasty surgery. This work presents AM technologies applied to design and manufacture of a biomodel, in fact, an implant for the surgical reconstruction of a large cranial defect. A series of computed tomography data was obtained and software was used to extract the cranial geometry. The protocol presented was used for creation of anatomic biomodel of the bone defect for the surgical planning as well as to design and manufacture of the patient-specific implant, reducing duration of surgery besides improving the surgical accuracy due to preoperative planning of the anatomical details.

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## 1. Introduction

Cranioplasty is one of the oldest performed surgical procedures. Archeological evidence suggests that ancient civilizations attempted to perform cranioplasties with materials such as gold, shells and gourds. Since then different materials have been employed, with variable success [1]. In present times, despite the development of better implantable materials, surgeons are still challenged by the need for safer and more precise reconstructions, especially in terms of recreating as normal a cranial tridimensional contour as possible. Titanium and its alloys have been widely used in the field of surgery for the construction of implantable devices.

Their biocompatibility has been extensively demonstrated, especially related to bone, both experimentally [2-5] and clinically with variable implant designs and methods of construction [6-9].

Additive manufacturing methods have been employed for a long time in fields where precise building of complex structures was necessary, such as aerospace engineering and racing cars development. These properties were more recently found useful in medical sciences, especially regarding biomaterials research, giving rise to studies of complex geometry implant construction. There is also some evidence of good osseointegration of titanium implants built by additive manufacturing in facial bone [10].

### 1.1. Additive manufacturing

Additive manufacturing (AM) or rapid prototyping (RP) is a fabrication technique by the additive method, i.e. based on successive addition of fine layers of material. This technology allows the production of physical components (prototypes, models, molds, etc) from information obtained directly from a three-dimensional geometric model CAD (Computer Aided Design) system. The process starts with the 3D computer model of the part, obtained by a CAD system, electronically sliced. From this slicing are obtained 2D contour lines which will define, in each layer, where material is going to be added or not. These layers are sequentially processed, generating the physical part through stacking and adhesion of them, beginning at the bottom and going up to the top part [11].

The construction of parts with complex geometry and in the most varied materials, the use of only one equipment to build the part from the beginning to the end, and less time and cost to obtain prototypes are some advantages that rapid prototyping offers when compared to other manufacturing processes [12].

In the medical field, additive manufacturing was integrated to digital imaging techniques of computed tomography (CT) and magnetic resonance (MR), making it possible to obtain solid biomodels that reproduce the anatomical structures. The internal structures images, acquired by these techniques, are handled in a system for medical imaging. From these images, specific algorithms of segmentation are applied to the separation of the interest structure (bone or tissue). From these image data, a 3D model is generated on the specific computer software (InVesalius or Mimics) and exported to be made by additive manufacturing, originating the biomodels (biomedical prototypes) [13].

These biomodels can be used for surgical planning, didactic purposes, the diagnosis and treatment of patients, and communication between professionals and patients. As a result, the biomodels facilitate surgery, reduce infection and rejection risks, complications and length of surgery [14-17].

Nowadays, the additive manufacturing allows also the design of customized prosthetic implants, suiting them directly to the patient's needs. It's possible to produce implants with sizes, shapes and mechanical properties optimized. For this, only digital information is used. All kinds of physical models are disregarded, obtaining directly the final implant and reducing the manufacturing time.

The use of these integrated techniques offers a significant potential of cost savings for health systems as well as the possibility to provide a decent life for a huge amount of people [18]. Additive manufacturing can be used for health professionals who work in orthopedics, neurosurgery, maxillofacial and orthognathic surgery and traumatology, craniofacial surgery and plastic, implant dentistry, oncology, among others.

The proposed solution is a way to make the use of the AM technology in planning surgical procedures viable, through the development and improvement of services, materials and equipment related to three-dimensional printing technology.

Surgical planning with the aid of Additive manufacturing allows the medical staff to have a physical model to evaluate, to plan and even simulate the surgical procedure before its performance. As a result, surgeries will be able to be

optimized and executed in shorter time, with less occupation time in the operating room, thus enabling significant cost savings to hospitals and lesser risks to the patient. Therefore, this solution can provide more security and reliability to the process as a whole.

An application in the medical field to be considered is the bone reconstruction surgery, for instance, the craniofacial reconstruction. Among the congenital defects, craniofacial anomalies are a group of highly diverse and complex that, together, affects a significant proportion of people in the world. Besides the cases of congenital deformities, there is an occurrence of acquired craniofacial defects due to other diseases, as tumors as well as due to trauma from accidents. In the last four decades, an increasing volume of cases of facial trauma was also observed, which is closely related with the increase of traffic accidents and urban violence. Additive manufacturing can also be used in prosthetic implants because the models provide information about size, direction and location of the implants, as well as anatomical information. In cases of bone abnormalities, it is important to note that the gain in patient's functional and psychological terms and the increased quality of life after surgery justify the costs of the application of new technologies.

There are more than 20 types of additive manufacturing systems on the market that, in spite of using different technologies of addition material, are based on the same principle of manufacturing by layer. The main additive manufacturing technologies used are stereolithography (SLA), selective laser sintering (SLS), direct metal laser sintering (DMLS), selective laser melting (SLM), fused deposition modeling (FDM), 3D printing (3DP) and electron beam melting (EBM). These systems are classified according to the initial state of raw material, which can be liquid, solid or powder form [19-20].

The additive manufacturing technique used in this work is the 3D printing (3DP) to create an anatomic biomodel of the bone defect for the surgical planning and, Direct Metal Laser Sintering (DMLS) the design and manufacture of the patient-specific implant. Among the advantages of DMLS technique, there is the ability to process titanium (TiCp and Ti64) and other metallic biomaterial (CoCr) directly on the machine.

## 2. Building Medical Model

The procedure for making 3D medical models (biomodels) using AM technologies implies few steps: patient selection, 3D digital image; Data transfer, processing and segmentation; Evaluation of design; and AM medical model production and validation.

### 2.1. Patient selection

A 39-year-old male patient was injured in Cerebrovascular Accident CVA with large post trauma defect in the right-frontal bone (Figure 1). The cranial section missing extended to an area of approximately 14.8 x 11.4 cm<sup>2</sup>. Following the initial management of the patient and the healing process, reconstruction of the cranial defect was required to restore the structural integrity of the skull and the patient's facial aesthetics.



Figure 1. Cranial large defect left frontoparietal-temporal bone.

Conventional cranioplasty is based on the open cold cure moulding technique and reconstruction of the implant on a freehand basis. Taking impressions of the defect directly through the patient's scalp is a major problem. Intraoperative moulding extends the duration of the operation and has been associated with complications due to localized tissue damage from the exothermic reaction during the material curing process. Furthermore, the limited intraoperative overview of larger osseous areas impedes judgment of symmetry. Conventional cranioplasty techniques are primarily based on the manual skills and experience of the surgeon. Only an accurately fabricated prosthesis fits into the defect properly and reduces the probability of subsequent movement, dislodgement and extrusion [21-22].

## 2.2. CT Digital Image

3D digital image can be obtained by using computer tomography - CT scanner or MRI data. These imaging technologies are used for modeling internal structures of human's body. Medical models made from this data must be very accurate and because of this, they require a spiral scanning technique which allows to do full volume scanning. This makes possible to generate a high number of slices (recommended thickness 1-2 mm) and what is very important, the pixel dimension in each slice could be reduced depending on each case. Most CT and MRI units have the ability of exporting data in common medical file format - DICOM – digital imaging and communication in medicine. After saving CT or MRI image data, they should be transferred to AM system. The next step is processing these data, which is a very complex and important step, with a significant impact on the quality of the final medical model.

For this step engineers need software package (for instance InVesalius) in which they can make segmentation of this anatomy image, achieve high resolution 3D rendering in different colors, make 3D virtual model and finally make possible to convert CT or MRI scanned image data from DICOM to .STL (structure triangularization language) file format. These software packages allow making segmentation by threshold technique, considering the tissue density. In this way, at the end of image segmentation, there are only pixels with a value equal or higher than the threshold value.

The virtual model of internal structures of human's body, which is needed for final production of 3D physical model, requests very good segmentation with a good resolution and small dimensions of pixels. This demands good knowledge in this field which should help engineers to exclude all structures

which are not the subject of interest in the scanned image and choose the right region of interest ROI (separate bone from tissue, include just part of a bone, exclude anomalous structures, noise or other problems which can be faced). Depending on complexity of the problem this step usually demands collaboration of engineers with radiologists and surgeons who will help to achieve good segmentation, resolution and a finally accurate 3D virtual model.

In image acquisition for biotemplating, the traditional tomographic technique is hardly changed, since the current standards for the craniomaxillofacial region already advocate thin slices. It was noted, however, that some caution is necessary when obtaining the images in order to improve them for later manipulation, namely:

- The gantry inclination must be avoided, because some biomedical prototyping software does not correct it;
- Metallic artifacts manufacturing, related to the tomographic technique, is worrisome as phantom images are going to be reproduced in the biomodel in case they are not manually edited in a long and tedious process. In this work, when editing is done by the radiologist in the radiology clinic in software without interface for Rapid Prototyping file format, these images cannot be sent completely edited for the prototyping service. This problem is due to the fact that the edition is only applied to 3D reconstruction displayed on screen, however, the sent images are the ones of 2D unedited cuts;
- The patient positioning with the occlusal plan parallel to the cut plan minimizes the production area of artifacts, keeping them almost restricted to the toothed region. If this positioning is not considered in patients with metal dental restorations, one can have as a result artifacts in various cuts, increasing the number of slices to be manually edited and therefore the time segmentation of images.
- Another important factor to be considered is the radiation dose related to CT scans. In the face region, this is an even more discussed factor, because the protocols for obtaining images typically involve a large number of cuts. Thus, when compared to other regions, the radiation dose for face exams is considered high. However, it is important to observe that in Radiobiology what matters is not total radiation dose of the exam, but its effective dose. In a maxillofacial region exam, this dose does not exceed biosecurity limits.

## 2.3. Segmentation and CAD design

Specific biomedical software is required to manipulate the images. Some softwares used in biomedical prototyping are Analyze ® (Mayo Foundation, USA), Mimics ® (Materialise, Belgium), and Biobuild ® (Anatomics, Australia). The mentioned software has some basic functions for processing and converting image files. They are necessary as the image files generated by the apparatus and CT (computer tomography) represent 2D cuts and are saved in the DICOM format. Nonetheless, for the manufacturing of a biomodel the station needs 3D files preferably in the STL format which is the standard format for manufacturing.

Currently, there is Brazilian free software, InVesalius from the ProMED project developed at CTI (Center for Information Technology Renato Archer) which meets the basic functions to integrate biomedical imaging equipment and AM, associated with imaging manipulation and three-dimensional visualization. Figure 2 shows the CT-images results of a skull segmentation of the patient through the system for medical imaging In Vesalius. After the segmentation, the 3D model should be converted into a format for additive manufacturing.

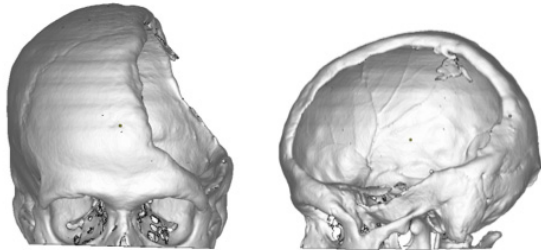


Figure 2. Virtual 3D model using InVesalius software.

The conversion of the 3D files to STL format, performed by biomedical software, generates an amount of triangles, so that it can adequately represent the complex topography of the craniomaxillofacial region. This can lead to some problems of file size coming to derail the process of manufacturing due to the processing required for slicing the model. For this reason, the STL file needs to be worked on specific software for AM such as Magics (Materialise).

The models coming from InVesalius are surface models that are build up out of facets (triangles). They are transferred through an STL-file. Conventional CAD-systems usually can import these files but in order to do operations on these data, it is necessary to convert the facet model into CAD-surfaces through the usually lengthy and difficult process of reverse engineering. For making surgical tools, incorporating other objects (fixation devices, implants), bone replacements, producing patterns for making fixtures or templates or other complex problems in different fields of medicine, this virtual model in IGES or STL format is processed using some CAD package. This is necessary for evaluation of design, quality of the made model, checking possible errors or other important steps which depends on the concrete case.

### 3. Additive manufacturing method for the Cranioplasty Surgery

Additive manufacturing is a relatively new technology capable of reproducing physical objects in various types of materials, from a virtual model, represented as data in a computer. The goal is to obtain a physical model with the same geometric characteristics of the virtual one, so that it can be manipulated for various purposes. One application that has emerged as highly promising is the reproduction of anatomical structures, through the image acquisition by medical imaging equipment, obtaining thereby the so-called biomodels to surgery aid.

The AM systems used in the case presented here includes two steps: (1) the creation of the medical biomodel using SLS system (EOS GmbH) and (2) the DMLS system (EOSint) for the design and manufacture of the customized implant required.

#### 3.1. Selective Laser Sintering (SLS)

An additive manufacturing layer technology, SLS involves the use of a high power laser (for example, a carbon dioxide laser) to fuse small particles of plastic into an object that has a desired three-dimensional shape. The laser selectively fuses powdered material by scanning cross-sections generated from a 3-D digital description of the part (for example from a CAD file or scan data) on the surface of a powder bed. After each cross-section is scanned, the powder bed is lowered by one layer thickness, a new layer of material is applied on top, and the process is repeated until the part is completed. The SLS machine preheats the bulk powder material in the powder bed somewhat below its melting point, to make it easier for the laser to raise the temperature of the selected regions the rest of the way to the melting point.

#### 3.2. DMLS process

The prosthetic implant was fabricated by the Direct Metal Laser Sintering (DMLS) technique using EOSINT M270 system. In DMLS technique, the powder is spread and processed by the action of an infrared laser in an inert and thermally controlled environment inside the chamber. A scanning mirrors system controls the laser beam describing the geometry of the layer on the surface of the spread material. With the incidence of the laser, the particles of material are heated and reach its melting point, joining each other and also to the previous layer. When the material solidifies, a new powder layer is added and the laser scans the desired areas once more, in other words, after the sintering of a layer, a new layer is deposited, and this process goes on until the construction of the part is finished. Thus, the implant is built layer by layer. The biomaterial powder of the Ti6Al4V alloy was used for the implant.

## 4. Results

#### 4.1. Creation of 3D virtual model of the patient skull

The patient was submitted to exam of computed tomography of the affected bone structure. For the exams, an acquisition protocol was used 1 mm for increment between slices and 1 mm of thickness, zero degrees of gantry inclination of the orientation.

Data obtained in the exams (DICOM format) were converted in 3D virtual model using InVesalius software (CTI-ProMED, Brazil). The software made possible to isolate woven of the bone structure through the segmentation for the threshold to export them in a STL file. The STL file was edited using Magics 15.0 software (Materialise, Belgium) in order to minimize surface imperfections.

This treatment enables a softening of the model in the upper skull region that containing more widely space slices.



#### 4.2. CAD system modeling to design the implant

For prosthesis generation, a subtraction Boolean was accomplished with 3D virtual model generated from the exam. This result bases prosthesis creation and fitting borders to refine seeking as better anchorage between prosthesis and bone. In order to create a perfect model for the implant, points from the symmetric right solid part of the head bone were used. Three key points in the nose were selected for the datum plane definition. These points were mirrored according to the created datum plane. Boolean operations were then applied to isolate the set of points required to reconstruct the cranial defect surface and produce the implant model. The new generated point cloud that defines the implant 3D geometry was processed to develop a CAD surface model. The commercial software SolidWorks was used for development of the implant CAD model (Figure 3).

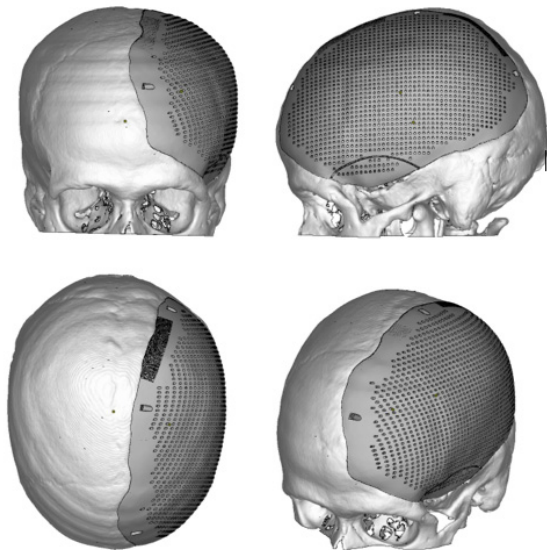


Figure 3. 3D CAD design for surgical device.

#### 4.3. Creation a biomodel and customized implant

The biomodel was constructed by 3D virtual model from computed tomography using SLS systems (EOS), and materials PA 2200. The biomodel was created based on the specifications of an anatomical drawing, in order to serve as a test before the surgery. In other words, it may be said that the biomodel is a virtual or real experiment that tries to mimic a real system. They can be used for teaching aims, in the manufacturing of customized prosthetic implants, in the early diagnosis and treatment of facial deformities, as well as to facilitate the communication between professionals and patients as well. Biomodels allow the measurement of structures, the simulation of osteotomies and of resection techniques, not to mention a complete planning of several types of craniomaxillofacial surgery. This tends to reduce the surgical procedure time and, as a result, the anesthesia period, as well as the risk of infection. There is also improvement in the result and reduction in the overall cost of the treatment.

The biocompatible implant fabricated using DMLS system based cranial reconstruction approach was an exact fit to the patient's cranial defect and produced a very symmetric skull outline. The material used was EOS Titanium Ti64 ELI (EOS GmbH, Germany), because it fulfills mechanical and chemical requirements of ASTM F 136 standard for surgical implant applications. This material has been used for implant and is inert. Ti64 ELI is it pre-alloyed Ti6Al4V and ELI (extra-low interstitial) version, which has particularly low level of impurities. The implant surface was finished by polishing and sterilization. The preoperative model and titanium implant are shown in Figure 4.

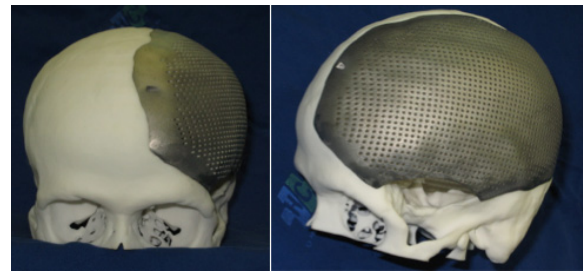


Figure 4. Biomodel and prostheses for cranio reconstruction surgery.

#### 4.4. Clinical application

During the surgical procedure using a conventional cranioplasty approach the patient custom made cranial reconstruction implant was placed onto the left frontoparietal-temporal bone and fixed with three screws. The surgery took about 2 hour. When reconstruction plate is formulated manually during operation this kind of surgery takes approximately 3 hours. The immediate outcome was successful and the implant fitted precisely onto the cranial large defect (Figure 5). The patient on the 8 month after surgery as shown in Figure 6.

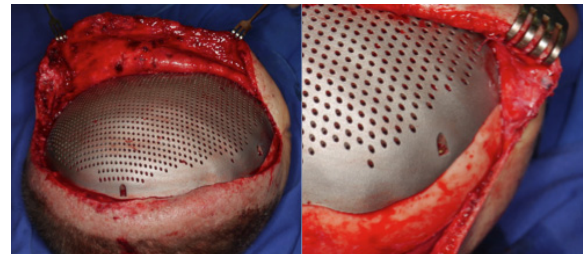


Figure 5. Prostheses to provide an aesthetically pleasing forehead contour.

#### 5. Conclusions

Additive Manufacturing (AM) medical models have found application for planning treatment for complex surgery procedures, training, surgical simulation, diagnosis, design and manufacturing of implants as well as medical tools. Additive manufacturing technique DMLS have been applied in the production of custom-built implants that meet the physical characteristics of each patient.



Figure 6. Patient on the 8 month after surgery.

The development of complex medical models and implant – virtual and physical – of a patient anatomical structure, from the digital images data acquired through hospital scanners, have proven to be a powerful tool for biomedical analysis and capability the design and manufacture of customized implants and prostheses prior to surgical procedures. This reduces duration of surgery due to preoperative planning of correct geometrical and anatomical details. The virtual and manufacturing processing also improves surgical accuracy and aesthetic results.

For futures directions in cranioplasty, the regenerative medicine can solve the problems of good integration of implants and protection of the underlying brain from infection. Implants may be cultured in a bioreactor along with recombinant growth factors to produce implants coated with bone progenitor cells and extracellular matrix that appear to the body as a graft, albeit a tissue-engineered graft. The growth factors would be left behind in the bioreactor and the graft would resorb as new host bone invades the space and is remodeled into strong bone, such advancements will lead to optimal replacement of cranial defects that are both patient-specific and regenerative.

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### References

- [1] Calderoni D. R. , Gilioli R., Jardini A. L., Maciel Filho R., Zavaglia C. A.C., Lambert C. S., Lopes E. S. N., Toro I. F. C., Kharmandayan, P., Paired evaluation of calvarial reconstruction with prototyped titanium implants with and without ceramic coating. *Acta Cirúrgica Brasileira - Vol. 29 (9) 2014*, 579.
- [2] Bandyopadhyay A, Espana F, Balla VK, Bose S, Ohgami Y, Davies NM. Influence of porosity on mechanical properties and in vivo response of Ti6Al4V implants. *ActaBiomater.* 2010 May;6(4):1640– 8. doi: 10.1016/j.actbio.2009.11.011
- [3] Vehof JWM, Haus MTU, de Ruijter AE, Spauwen PHM, Jansen J a. Bone formation in transforming growth factor beta-I-loaded titanium fiber mesh implants. *Clin Oral Implants Res.* 2002 Mar;13(1):94– 102. doi: 10.1034/j.1600-0501.2002.130112.x
- [4] Ponader S, von Wilmowsky C, Widenmayer M, Lutz R, Heint P, Körner C, Singer RF, Nkenke E, Neukam FW, Schlegel KA. In vivo performance of selective electron beam-melted Ti-6Al-4V structures. *J Biomed Mater Res A.* 2010 Jan;92(1):56–62. doi: 10.1002/jbm.a.32337
- [5] Warnke PH, Douglas T, Wollny P, Sherry E, Steiner M, Galonska S, Becker ST, Springer IN, Wiltfang J, Sivananthan S. Rapid prototyping: porous titanium alloy scaffolds produced by selective laser melting for bone tissue engineering. *Tissue Eng Part C Methods.* 2009 Jul;15(2):115–24. doi: 10.1089/ten.tec.2008.0288
- [6] Neovius E, Engstrand T. Craniofacial reconstruction with bone and biomaterials: review over the last 11 years. *J Plast Reconstr Aesthet Surg.* 2010 Oct;63(10):1615–23. doi: 10.1016/j.bjps.2009.06.003
- [7] Cabraja M, Klein M, Lehmann T-N. Long-term results following titanium cranioplasty of large skull defects. *Neurosurg Focus.* 2009 Jul;26(6):E10. doi: 10.3171/2009.3.FOCUS091
- [8] Kuttenger JJ, Hardt N. Long-term results following reconstruction of craniofacial defects with titanium micro-mesh systems. *J Craniomaxillofac Surg.* 2001 Apr;29(2):75–81. doi:10.1054/jcms.2001.0197
- [9] Joffe J, Harris M, Kahugu F, Nicoll S. A prospective study of computer-aided design and manufacture of titanium plate for cranioplasty and its clinical outcome. *Br J Neurosurg.* 1999 Dec;13(6):576-80. PMID: 10715726
- [10] Goiato MC, Santos MR, Pesqueira AA, Moreno A, dos Santos DM, Haddad MF. Prototyping for surgical and prosthetic treatment. *J Craniofac Surg.* 2011 May;22(3):914–7. doi: 10.1097/SCS.0b013e31820f7f90
- [11] Gibson I, Cheung LK, Chow SP, Cheung WL, Beh SL, Savalani M, Lee SH: The use of rapid prototyping to assist medical applications. *Rapid Prototyp. J.* 12: 53 58,2006.
- [12] Hieu LC, Bohez E, Sloten, FV, Phien HN, Vatcharaporn E, Binh PV, OrisP :Design for medical rapid prototyping of cranioplasty implants. *Rapid Prototyp. J.* 9: 175 186, 2003.
- [13] Truscott M, Beer D, Vicatos G, Hosking K, Barnard L, Booysen G, Campbell RI: Using RP to promote collaborative design of customised medical implants. *Rapid Prototyp. J.* 13: 107 114, 2007.
- [14] Wu W, Zhang Y, Li H, Wang W: Fabrication of repairing skull bone defects based on the rapid prototyping. *J. Bioact. Compat. Polym.* 24: 125 136, 2009.
- [15] Oliveira RS, Brigato R, Madureira JF, Cruz AA, Mello Filho FV, Alonso N, Machado HR: Reconstruction of a large complex skull defect in a child: a case report and literature review. *Child's Nerv. Syst.* 23: 1097 1102, 2007.
- [16] Gopakumar S: RP in medicine: a case study in cranial reconstructive surgery. *Rapid Prototyp. J.* 10 :207 211, 2004. [17] Bertol LS: Medical design: Direct metal laser sintering of Ti-6Al-4V. *Mater. Des.* 31: 3982 3988, 2010.
- [17] Bertol LS: Medical design: Direct metal laser sintering of Ti-6Al-4V. *Mater. Des.* 31: 3982 3988, 2010.
- [18] Singare S, Lian Q, Wang WP, Wang F, Liu Y, Li D, Bingheng L: Rapid prototyping assisted surgery planning and custom implant design. *Rapid Prototyp. J.* 15: 19 23, 2009.
- [19] Milovanović J, Trajanović M: Medical applications of rapid prototyping. *Mechanical Engineering* 5: 79 85, 2007.
- [20] Khan SF, Dalgarno KW: Design of customized Medical Implants by Layered Manufacturing. School of Mechanical and Systems Engineering, NC University, UK, 2009.
- [21] Maravelakis E, David K, Antoniadis A, Manjos A, Bilalis N, Papaharilaou Y: Reverse Engineering Techniques for Cranioplasty: A Case Study. *Journal of Medical Engineering & Technology* 32: 115 121, 2008.
- [22] Muller A, Krishnan K, Uhl E, Mast G: The Application of Rapid Prototyping Techniques in Cranial Reconstruction and Preoperative Planning in Neurosurgery. *Journal of Craniofacial Surgery* 14: 899 914, 2003.